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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,070	01/29/2002	Thomas C. Evans	NEB-177-PUS	4532
28986	7590	06/02/2004	EXAMINER	
NEW ENGLAND BIOLABS, INC.			SCHNIZER, HOLLY G	
32 TOZER ROAD			ART UNIT	
BEVERLY, MA 01915			PAPER NUMBER	

1653

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/937,070	<b>Applicant(s)</b> EVANS ET AL.	
	<b>Examiner</b> Holly Schnizer	<b>Art Unit</b> 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 29 January 2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-16 and 18 is/are rejected.
- 7) ☐ Claim(s) 17 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/15/01</u> . | 6) <input type="checkbox"/> Other: _____  |

**DETAILED ACTION**

***Status of the Claims***

Claims 1-18 are pending and have been considered on the merits in this Office Action.

***Priority***

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The present case is a 371 of an international application and the Declaration filed January 29, 2002 in the present application, indicates priority to provisional Application No. 60/180,319.

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). For example, a statement reading "This Application is a 371 of PCT/US01/03147, filed January 31, 2001 and claims the benefit of U.S. provisional application No. 60/180,319, filed February 4, 2001" should be entered following the title of the invention or as the first sentence of the specification.

For the purposes of this Office Action, the effective filing date of the present application has been considered to be January 29, 2001.

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### ***Specification***

The abstract of the disclosure is objected to because the abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. Correction is required. See MPEP § 608.01(b) and 37 CFR 1.72(b).

### ***Claim Rejections - 35 USC § 112***

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "said first and second polypeptides" in line 1. There is insufficient antecedent basis for this limitation in the claim with respect to its dependency on Claim 12 (Claim 12 does not refer to "first and second polypeptides". Correction is required.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 12, 14, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Scott et al. (Proc. Natl. Acad. Sci. (Nov. 1999) 96(24): 13638-13643; ref. CN of IDS filed 10-12-01).

Scott et al. teach a method for the in vivo production of cyclic peptides and proteins. In the method of Scott et al., the C-terminal portion of the naturally split Ssp DnaE intein is fused to the N-terminus of dihydrofolate reductase (DHFR, a target enzyme) or Pseudostellarin F (a target protein) and the N-terminal portion of the Ssp DnaE intein is fused to the C-terminus of DHFR (see Fig. 1, 2, and p. 13640, Col. 1, 3<sup>rd</sup> paragraph) or the C-terminus of Pseudostellarin F (Fig. 2e and f and p. 13641, Col. 1, 2<sup>nd</sup> section). The fused polypeptide was reacted in vivo and resulted in the formation of a cyclic polypeptide in vivo (see p. 13641, 2<sup>nd</sup> Col., last paragraph and Table 1).

Claims 1-16 and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Evans (J. Biol. Chem. (March 2000) 275(13): 9091-9094).

Evans et al. show successful in vitro trans-splicing between two proteins, MBP-DnaE(N)-CBD and CBD-DnaE(C)-T4 DNA ligase to yield a spliced protein, MBP-T4 DNA ligase (ML) (p. 9093, Col. 2, last paragraph; Fig. 4B; and p. 9094, Col. 2, lines 7-10). Evans et al. report that little difference in splicing efficiency was observed when chitin bound or free ME(N)B was used to react with the chitin-bound BE(C)L (sentence spanning pp. 9093-9094). The fused protein was eluted from the solid support (Fig. 4B, lane 8). MBP (considered "a first polypeptide") is a protein and T4 DNA ligase (considered "a second polypeptide") is an enzyme. Both polypeptides were immobilized

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on chitin beads (an affinity based support) (p. 9093, Fig. 4 and legend). The first and second intein fragments used in the method of Evans were the N- and C-terminal fragments of a naturally split Ssp DnaE intein (p. 9094, Col. 2). The intein fragments used in the method of Evans et al. contain a chitin binding domain (CBD) (p. 9093, Col. 2, last paragraph). The fusion constructs of Evans et al. include a construct wherein the N-terminal intein fragment is fused to the C-terminus of the first polypeptide (MBP-DnaE(N)-CBD) and a construct wherein the C-terminal intein fragment is fused to the N-terminus of the second polypeptide (MBP-CBD-DnaE(C)-T4 DNA ligase) (see p. 9093, last paragraph).

Evans et al. also describes a methods for producing a cyclic polypeptide in vivo or on an affinity column comprising fusing the C-terminal portion of a naturally split intein to the N-terminus of a target polypeptide and fusing the N-terminal portion of a naturally split intein to the C-terminus of the target polypeptide to produce a fused polypeptide. For in vivo production, the fused polypeptide is reacted in vivo under conditions to form a cyclic protein (Fig. 5A and figure legend). For the in vitro production on an affinity column, a chitin binding domain is fused to the fused polypeptide (see Fig. 3B), the intein (C)-target protein-intein(N)-CBD fusion protein is immobilized on chitin beads (an affinity based support) (Fig. 5B), and incubating the immobilized precursor under conditions that favor formation of a cyclic polypeptide. Evans et al. also describe eluting the cyclic protein from the solid support (Fig. 5B, lane 5; see fig. Legend).

The examiner notes that since the publication date of the Evans et al. reference is March 2000, the above rejection could be overcome by claiming priority to provisional application number 60/180,319.

### ***Claim Objections***

Claim 17 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### ***Conclusions***

No Claims are allowable. Claims 1-16 and 18 are rejected for the reasons stated above. Claim 17 is objected to.

A search of the prior art did not reveal any methods having steps identical to Claims 11 or 12 wherein an artificially split intein is used. Thus, Claim 17 would be allowable if amended as suggested to overcome the objection above. Iwai et al. (J. Biol. Chem. (2001) 276(19): 16548-16554) is considered to teach the method of Claim 17, however Iwai et al. was published just after the filing date of the present Application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Holly Schnizer  
May 28, 2004



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